Calorically Dense Nutritional Composition

This invention relates generally to the treatment and nutritional support of mammals. More specifically, the present invention relates to compositions for use in metabolically stressed patients who need food restriction, but who do not necessarily need increased contents of protein or special nutrients.

Patients suffering from a loss of nutrients require adequate nutritional support. A lack of adequate nutritional support can result in malnutrition associated complications. Thus, the goal of nutritional support is to maintain body mass, provide nitrogen and energy in adequate amounts to support healing, meet metabolic demands characterised by the degree of stress, and support immune function.

A traditional form of nutritional support is administering whole protein liquid feedings to the patient to remedy the protein deficiency. However, some patients requiring nutritional support have a compromised absorptive capacity and thus cannot tolerate whole protein liquid feedings as well as the long-chain fatty acids and complex carbohydrates often present in such whole protein feedings. Many diseases or their consequences can cause malabsorption by impairment of either digestion or absorption. For instance, patients suffering from various types of inflammatory bowel diseases typically cannot tolerate whole protein feedings. As a result, semi-elemental and elemental protein diets were developed to treat such compromised patients.

However, in addition to the traditional inflammatory bowel type patients, semi-elemental and elemental protein diets are currently being used in other patient segments. Specific conditions where these diets are being used include, for example, total parenteral nutrition patients receiving early transitional feedings, acutely ill, and catabolic patients with increased nitrogen needs yet requiring an elemental diet.

Still further, many patients suffering from metabolic stress have a significant need for increased energy but often do not need or tolerate protein levels beyond the normal requirement. Such patients also cannot tolerate the food volume necessary to deliver the energy they need. As a result, such patients need an elemental diet that provides calorically dense nutritional support while at the same time providing moderate non-protein calories per gram of nitrogen. Although a variety of elemental and semi-elemental diets are currently being used in an attempt to treat and/or provide nutritional requirements to such

patients, the needs of the metabolic stressed patients are not being adequately met.

Accordingly, a need exists for an enteral nutritional formulation that meets the nutrient requirements of metabolically stressed patients without unnecessarily subjecting such patients to high fluid volume treatments or formulations with increased protein levels.

In one aspect, this invention provides an enteral composition composition designed for metabolically stressed patients; human and animal. The enteral composition comprises: a protein source providing about 15% to about 20% of the energy of the composition; a carbohydrate source; and a lipid source including a mixture of medium and long chain triglycerides, the enteral composition having a caloric density of at least about 1.4 kcal/ml.

The enteral composition provides nutritional support in the form of increased energy density without elevated protein levels or excess fluid. In particular, the enteral composition, unlike prior compositions, has an energy density of at least about 1.4 kcal/ml.

Preferably, the enteral composition provides energy dense nutritional support while at the same time providing moderate non-protein calories per gram nitrogen (NPC/gN). Specifically, the enteral composition has a clinically acceptable ratio of non-protein calories per gram nitrogen of at least approximately 90:1; for example about 140:1 to about 100:1.

In an embodiment, the hydrolysed protein source is hydrolysed whey protein.

In another aspect, this invention provides an enteral composition for a metabolically stressed patient comprising: about 15% to about 20% of the energy of the composition of partially hydrolysed whey protein; a carbohydrate source; and a lipid source including a mixture of medium and long chain triglycerides; the composition having an energy density of at least about 1.4 kcal/ml and a ratio of non-protein calories per gram of nitrogen of at least about 90:1

In another embodiment, the lipid source of the composition includes at least 70% medium chain triglycerides.

Moreover, due to the calorically dense nature of the enteral composition, the enteral composition may include 100% of U.S. RDA of vitamins and minerals in about 1500 kcal (1000 ml).

Preferably, the composition is in ready-to-use form, is nutritionally complete, and contains proteins, lipids, vitamins and minerals in proportions

suitable for older children (10+ years) and adults. The enteral composition may be fed by tube or orally.

The invention also provides a method for providing nutrition to a metabolically stressed patient. The method includes administering to the patient a therapeutically effective amount of a composition having an energy density of at least about 1.4 kcal/ml. The composition with such increased energy density includes a protein source comprising approximately 15% to 20% of the energy of the composition, a carbohydrate source, and a lipid source including a mixture of medium and long chain triglycerides.

The composition is be especially useful for patients using the composition as a supplement (i.e. HIV, cystic fibrosis) and as a nocturnal feeding (cystic fibrosis).

Additional features and advantages of the invention are described in, and will be apparent from, the detailed description of the presently preferred embodiments.

Nutritional support of hospitalised as well as non-hospitalised patients requires prevention, recognition and treatment of nutritional depletion that may occur with illness. The goals of nutritional support include stabilising metabolic state, maintaining body mass, and/or facilitating growth in the presence of disease and gastrointestinal dysfunction.

Certain disease states exist that alter intake, absorption or metabolism. For example, certain health conditions can impair the nutrient absorption and/or reduced gastrointestinal tolerance for diets which are based on whole proteins. These conditions include patients suffering specifically from a compromised gut function as well as patients, due to the severity of their condition, who are simply unable to tolerate whole protein diets.

Moreover, although certain patients with impaired nutrient absorption and/or reduced gastrointestinal tolerance may need fluid restriction, such patients do not necessarily need the increased contents of protein or special nutrients often present in existing elemental diets. For instance, patient groups suffering from Crohn's disease, cancer, cystic fibrosis, short bowel syndrome, cerebral palsy, intractable diarrhoea, gastric reflux and HIV/AIDS often are classified as falling within this group of patients. Likewise, patients transitioning from parenteral feeding, are acutely ill, or are considered post-surgery with cardiac/renal complications requiring fluid control also have a need for increased energy, but often do not need or tolerate protein levels beyond normal

requirements and cannot tolerate the fluid volume necessary to deliver the needed energy. For purposes of the present application, this population of patients are generically referred to as metabolically stressed patients.

This invention provides a product that is specifically directed to meet the nutritional needs of metabolically stressed patients without elevated protein levels or excess fluid. To this end, the invention provides calorically dense nutritional support in the form of an enteral composition while at the same time providing a moderate NPC/gN ratio. The composition preferably utilises hydrolysed whey protein, medium chain triglycerides and maltodextrin to enhance absorption in the metabolically stressed patients.

The protein source provides approximately 15% to 20% of the total energy of the composition; for example about 15% to 18%. In an embodiment, the protein source comprises approximately 16% (4 g/100 kcal) of the total energy of the composition. For adults and older children (10+ years old), the protein concentration is optimal for the moderate tissue repair needs of the targeted patient populations without imposing an undue nitrogen burden on renal function.

The composition is preferably a peptide-based diet to maximise tolerance and absorption. In an embodiment, the protein source includes enzymatically hydrolysed whey protein. In a preferred embodiment, the protein source is hydrolysed whey protein. This type of protein source reduces the incidence of gastric reflux because gastric emptying is faster than with diets containing casein or whole whey.

Also, the hydrolysed whey protein serves as a rich source of the amino acid cysteine. Cysteine is a limiting amino acid for the formation of glutathione, and endogenous glutathione needs are greater in patients with chronic inflammatory and infectious conditions. The composition preferably contains approximately 0.1% to 0.8% of energy as cysteine. In a preferred embodiment, the composition contains approximately 0.37% of energy as cysteine (925 mg/1000 calories).

The protein source may also include a portion as free amino acids. As with protein hydrolysate, the use of free amino acids reduces the potential for nutrient malabsorption. In an embodiment, the protein source contains from about 0.1% to 2.0% of energy of free amino acids. Preferably, the protein source of the present invention contains less than about 2% of energy of free amino acids.

Carbohydrates provides, in an embodiment, approximately 35% to 65% and, most preferably, approximately 40% to 60% of the energy of the composition. In an embodiment, the carbohydrate source provides about 51% of the energy of the composition. A number of carbohydrates may be used. By way of example, the carbohydrates can be chosen from maltodextrin, corn starch, sucrose and corn syrup solids.

The lipid source may includes a mixture of medium chain triglycerides (MCT) and long chain triglycerides (LCT). The lipid source invention provides about 20% to about 50% of the energy of the composition; preferably about 25% to about 40%. In an preferred embodiment, the lipid source provides about 33% of the energy of the composition.

The lipid profile is designed to meet essential fatty acid needs (omega-3 and omega-6) while also keeping the medium-chain triglyceride (MCT) content high and long-chain triglyceride (LCT) content low compared with prior formulas. Preferably, the lipid source comprises approximately 30% to 80% by weight MCTs. In a preferred embodiment, the lipid source includes about 70% by weight from MCTs. MCTs are easily absorbed and metabolised in the metabolically stressed patient. The use of MCTs will also reduce the risk of potential for nutrient malabsorption. In a preferred embodiment, the medium chain triglyceride source is fractionated coconut oil.

The remainder of the lipid source is a mixture of LCTs. Suitable sources of LCT's are canola oil, corn oil, soy lecithin and residual milk fat and soybean oil. The lipid profiles containing such LCTs are designed to have a polyunsaturated fatty acid omega-6 (n-6) to omega-3 (n-3) ratio of about 1:1 to 10:1; preferably about 6:1 to about 9:1. The proposed ratio of n-6:n-3 is designed to reduce the immune suppression associated with high omega-6 fatty acid concentration and provide adequate essential fatty acid. In an embodiment, the composition includes an omega-6 to omega-3 ratio of about 7:1.

Still further, the composition contains a specialised vitamin and mineral profile. The composition may include at least 100% of the United States Recommended Daily Allowance (USRDA) of vitamins and minerals in 1500 kcal. Moreover, the composition includes higher levels of key vitamins and minerals designed to support the metabolically stressed patients.

Specifically, the composition may include a high level of zinc. Preferably, at least approximately 225% of the USRDA of zinc is provided in the composition per 1500 Kcal. In an embodiment, 28.5 to 43.5 mg per 1500

calories of zinc are provided. In a preferred embodiment, 36 mg per 1500 calories of zinc is provided. The increased zinc compensates for zinc losses and provides increased zinc for tissue repair in a patient having increased healing requirements.

The composition may also include an increased amount of vitamin C. At least approximately 750% of the USRDA of vitamin C is provided per 1500 Kcal. In an embodiment, 405 to 615 mg per 1500 calories of vitamin C is provided. In a preferred embodiment, 510 mg per 1500 calories of vitamin C is provided. Vitamin C is believed to accelerate the healing and granulation in patients with severe healing requirements. Vitamin C will support increased requirements/losses after surgery.

The composition may also include increased amounts of selenium. Selenium deficiencies may develop in patients having elevated healing requirements. At least approximately 60 to 90 μg of selenium may be provided in 1500 calories of composition. In a preferred embodiment, approximately 75 μg of selenium per 1000 calories is provided.

Many of the commercially available enteral formulas contain far below the amount of carotenoids (beta-carotene) found in usual diets of normal healthy people. In fact, patients on liquid formula diets as their sole source of nutrition for one week or more have been found to have plasma concentrations of carotenoids of only 8% to 18% as compared to controls consuming a free choice of diet (Bowen et al, "Hypocarotenemia in Patients Fed Enterally with Commercial Liquid Diets," *Journal of Parenteral and Enteral Nutrition*, 12(5): 44-49 (1988)). Those on enteral formulas for more than three weeks have negligible concentrations of any common serum carotenoids.

To meet these requirements, the composition may include a source of β-carotene. β-Carotene is added to the composition to normalise beta-carotene serum plasma levels and to avoid beta-carotene deficiency in long term tube-fed patients. β-Carotene also meets a portion of the required Vitamin A, thereby meeting micro-nutrient requirements in a small caloric volume. Moreover, β-carotene is an important nutrient with anti-oxidant properties. The composition may include approximately 1.25 to 4.0 mg per 1500 kcal of β-carotene. In a preferred embodiment, the composition includes approximately 1.52 mg of β-carotene per 1500 kcal of the composition. This amount prevents deficiencies and provides for possible increased requirements in the healing patient.

Moreover, the β-carotene and vitamin A levels allow plasma concentrations of retinol to be increased to near normal optimal levels of 500 mcg per litre.

The composition may also include increased amounts of L-carnitine and taurine to support the increased requirements of the acutely ill, catabolic patient. Both taurine and L-carnitine are preferably present in amounts of approximately 120 to 180 mg per 1500 calories. In preferred embodiments, both taurine and L-carnitine are present in an amount of approximately 150 mg per 1500 calories.

Still further, the composition may include decreased amounts of magnesium. Magnesium has been associated with diarrhoea. In an embodiment, magnesium is present in an amount of approximately 308 mg to 462 mg per 1500 calories. In a preferred embodiment, magnesium is present in an amount of approximately 400 mg per 1500 calories.

The composition may be in any suitable form such as ready-to-use liquid form and powder form. The composition can provide the total nutritional requirements of the metabolically stressed patient or can act as a supplement. The composition can be tube-fed to a patient, or fed by having the patient drink it. For instance, the composition can be provided in cans or a spike and hang bag. The composition is preferably ready-to-use and does not require reconstitution or mixing prior to use.

Unlike prior formulations, the composition provides calorically dense nutritional support while at the same time providing a moderate NPC/gN ratio. To this end, the composition preferably has a caloric density of approximately 1.4 to 1.8 kcal/ml. For example, the composition has a caloric density of about 1.5 kcal/ml. The composition provides a moderate NPC/gN ratio of at least about 90:1. For example, the composition provides a NPC/gN ratio of about 140:1 to about 100:1. Preferably, the composition provides a NPC/gN ratio of 131:1.

Furthermore, unlike prior formulations, the composition has a low osmolality of approximately 375 to 600 mOsm/kg H_2O in an unflavoured product. The osmolality of the composition in a flavoured product is approximately 500 to 700 mOsm/kg H_2O.

The composition may be utilised to treat metabolically stressed patients. As used herein, metabolically stressed patients are patients who, due to either a disorder or condition, are unable to tolerate whole protein diets and need fluid restriction, while at the same time cannot tolerate elevated protein levels or excess fluid. For example, the composition may be utilised to provide nutrition

to critically ill patients transitioning from total parenteral nutrition therapy and acutely ill, catabolic patients. Moreover, the composition can be utilised to provide nutrition to patients suffering from the following conditions and/or diseases; Crohn's disease; cystic fibrosis; HIV/AIDS; cancer; patients of post-surgery with cardiac/renal complications requiring fluid control; intractable diarrhoea; short bowel syndrome; cerebral palsy; and gastric reflux.

Of course, it will be appreciated that a variety of compositions are possible. An example of a composition has a caloric density of about 1.5 kcal/ml. This is equivalent to 375 kcal/250 ml which will, in a preferred embodiment, be one unit (can or container) of product.

Example 1

The composition includes the following ingredients: water; maltodextrin, enzymatically hydrolysed whey protein, medium-chain triglycerides (MCT source: fractionated coconut oil); corn starch; soy bean oil; soy lecithin; potassium phosphate; guar gum; calcium citrate; sodium phosphate; choline chloride; sodium chloride; calcium phosphate; calcium ascorbate; magnesium chloride; potassium citrate; magnesium oxide; potassium chloride; taurine; citric acid; L-carnitine; zinc sulphate; ferrous sulphate; DL-alpha tocopherylacetate; nicotinamide; retinyl palmitate; calcium pantothenate; manganese sulphate; copper sulphate; pyridoxine hydrochloride; riboflavin; thiamine; folic acid; cholecal ciferol; biotin; potassium iodide; β-carotene; sodium molybdate; chromium chloride; phylloquinone; sodium selenate; and cyanocobalamin.

The composition may have the following nutrient composition (per 1500 calories (1000 ml)):

Nutrient Composition	Amount	% U.S. RDA*
Protein	60.0 g	132
Carbohydrate	191.0 g	**
Lipid***	58.5 g	**
Water	780 ml	**
Vitamin A	6000 IU	100
Beta-Carotene	3.0 mg	**
Vitamin D	600 IU	148
Vitamin E	45 IU	148
Vitamin K	75 mcg	**
Vitamin C	510 mg	840
Thiamine (B_1)	3.0 mg	200
Riboflavin (B_2)	3.6 mg	212
Niacin	42 mg	208
Vitamin B_6	6 mg	300
Folic Acid	810 mcg	136
Pantoth. Acid	21 mg	140
Vitamin B_{12}	12 mcg	132
Biotin	600 mcg	132
Choline	675 mg	**
Taurine	150 mg	**
L-Carnitine	150 mg	**
Calcium	1000 mg	100
Phosphorus	1000 mg	100
Magnesium	400 mg	100
Zinc	36 mg	240
Iron	27 mg	148
Copper	3.0 mg	148

Nutrient Composition	Amount	/ U.S. RDA*
Manganese	4.0 mg	**
Iodine	225 mcg	148
Sodium	1020 mg	**
Potassium	1872 mg	**
Chloride	1740 mg	**
Chromium	60 mcg	**
Molybdenum	180 mcg	**
Selenium	75 mcg	**

* U.S. Recommended Daily Allowance for Adults & Children 4 or more years of age

** U.S. RDA not established

*** MCT provides 40.8 grams/1000 ml

In this example, the protein source comprises essentially 100% hydrolysed whey protein. The carbohydrate source preferably includes approximately 70% to 95% maltodextrin, from about 5% to 15% corn starch, and up to about 20% sucrose; all % being on the basis of energy. Lastly, the lipid source preferably includes approximately 70% MCTs, approximately 17% soybean oil; approximately 8% residual milk fats; and approximately 5% soy lecithin; all % being on the basis of weight.

Example 2

The composition of example 1 is evaluated in a group of severely traumatised patients requiring early enteral feeding. Patients are fed by small bowel feeding tubes. The goal of this early feeding is to supply at least 60% of their calculated energy needs. The primary data collected to evaluate this early feeding is to determine the tolerance to early and fairly aggressive feeding. Gastrointestinal symptoms such as diarrhoea, bloating and cramping are tabulated and evaluated. Actual intake as a percentage of calculated energy requirements is calculated for each patient on each day of feeding for five

consecutive days. The nutritional goals set are 25 kcal/kg of estimated body weight/day and 1.6 grams of protein/kg/day.

Eighteen (18) patients are entered into the study and 16 of these patients complete the 5 days of feeding. For the first 24 hours of feeding, the average intake for the 16 patients is 65 ± 12% of the calculated nutritional requirement. The intake over the first 48 hours of feeding is 68 ± 8% of requirements. Over the first 72 hours of feeding, the average intake is 73 ± 6% of requirements and for the first 96 hours of feeding, the mean intake typically rises to 87 ± 6% of requirement. Over the full five days of feeding evaluation, the average intake is 92 ± 7% of the calculated energy requirements for the 16 patients who completed the full study period. Diarrhoea develops in only one patient in the group and this generally persists for approximately 18 hours. No other gastrointestinal symptoms would typically be reported during the study period.

It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the invention and without diminishing its attendant advantages. It is therefore intended that such changes and modifications be covered by the appended claims.